A Review of the Novel Treatments for Alzheimer's Disease

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Introduction

Alzheimer's disease (AD) is a brain disorder that gradually destroys thinking skills, memory, and other mental functions. The number of individuals diagnosed with AD is growing rapidly with more than 6 million Americans of all ages having the disease. It is the fifth-leading cause of death among adults over 65 and the sixth-leading cause of death for all adults in the nation. Women currently have a higher lifetime risk than men, and although AD is so harmful, it is still incurable.

Although the exact causes of AD are unknown, it is currently characterized by two abnormalities in the brain: amyloid plaques and neurofibrillary tangles. Amyloid-beta is a protein whose function isn't completely understood but is thought to be produced in many cells as well as nerve cells, or neurons because it plays a critical role in normal cell development and maintenance. However, in AD, the enzymes that break down these proteins become less effective or impaired. As a result, an unusual amount of amyloid-beta builds up, forming plaques in the tissues between neurons. Neurofibrillary tangles are abnormal accumulations of the protein tau. In healthy neurons, tau is a microtubule-associated protein, meaning that it stabilizes the microtubules and ensures proper communication and transport between the neurons. In AD, abnormal chemical changes cause the tau protein to twist into pairs of helical filaments that collect into tangles. When this happens, the microtubules cannot function properly and they disintegrate. This collapse of the neuron's transport system impairs communication between the neurons and causes them to die.

This neuronal degradation results in slower communication between cells and therefore slower mental processes: individuals usually experience dementia (memory loss), impaired language and judgment, and slower thinking abilities.

Alzheimer's disease remains a significant concern as it currently lacks a cure. To address this pressing issue, this review delves into a wide range of novel treatments that are under investigation. These treatments encompass diverse approaches, from nonpharmacological interventions like exercise and meditation to treatments such as medication and brain stimulation. By shedding light on the ongoing research efforts, this paper aims to highlight the promising avenues being explored to find effective treatments for Alzheimer's disease.

Treatments

Effect of Aerobic Exercise

Aging is a major contributor to Alzheimer's disease. As individuals get older, their neurons slowly start to deteriorate, making them more vulnerable to the effects of amyloid-beta and tau build-up. Many patients also experience Mild Cognitive Impairment (MCI), a condition in which individuals experience memory loss and slower thinking. It is often a biomarker for AD. A study by Baker et al. (2010) found that aerobic exercise can improve cognitive function in elderly people with MCI, especially women. The study participants, running from ages 55-85, engaged in aerobic exercise for 6 months, while a control group did stretching exercises.

Participants completed a series of assessments at baseline and after 6 months. For example, the cardiorespiratory fitness assessment, an exercise treadmill test, measured peak oxygen consumption. The cognitive assessment portion included tests of executive function and short-term memory such as a Trail Making Test, Stroop Color and Word Test, Verbal Fluency Test, and List Recalling Test.

The results showed that six months of controlled aerobic exercise improved executive function, cognitive flexibility, information processing efficiency, and selective attention. The aerobic group, on average, performed better than the control group in most tests. In the Trails B test, the aerobic group was faster to complete the task relative to baseline whereas the stretching control group tended to be slower.

In terms of sex differences, for women, increasing VO2 max was associated with improved executive function. The Stroop test also showed that performance increased for women in the aerobic group after six months. Glucoregulation and insulin sensitivity also improved with aerobic exercise for women but not for men. In addition, relative to controls, aerobic exercise reduced cortisol levels for women and increased levels for men.

This study shows the high efficacy of nonpharmacological treatments and that it is a viable treatment option for AD.

Effects of Creative Therapy

Perhaps because MCI is at the early end of AD, there are multiple nonpharmacological approaches for treatment. In addition to exercise programs, studies have shown that novel cognitive programs like Timeslips, which use storytelling and creative expression (CrExp), have demonstrated promise in slowing cognitive decline. This study aims to explore the effects of a

CrExp program, including storytelling and drawing tasks, on cognitive functioning in older adults with MCI (Zhao 2018).

The study was a 16-week clinical trial conducted with participants who were adults aged 60 or older. To be included in the study, patients had to meet specific criteria for mild cognitive impairment (MCI), including cognitive complaints, objective cognitive impairment, and normal daily living abilities. They were randomly assigned to either the CrExp group or a control group (CG).

The cognitive program for the CrExp group involved a total of 25 sessions over 16 weeks, facilitated by a group of professional therapists. All sessions began with a 5–10 min warm-up of an interaction game, followed by a 10 min drawing and then a 30 min core CrExp. The CG participated in standard cognitive rehabilitation, which involved a total of the same sessions as the CrExp group over 16 weeks, facilitated by a group of occupational therapists. Each session included 10 min of “finger exercises”, 28 followed by 30 min of an activity or game, and, finally, 5 min of conclusion speeches.

Chinese variations of cognitive assessments (Montreal Cognitive Assessment, Auditory Verbal Learning Test, Trail Making Test B, etc.) were given baseline, postintervention, and 6 months follow-up to test general cognitive function including memory, attention, and executive function.

The results showed that the CrExp group showed superior improvements in general cognitive functioning, memory, executive functioning, attention, and daily living abilities compared to the control group both immediately after the intervention and at the 6-month follow-up.

Effects of Meditation and Music Listening

Blood biomarkers implicated in cognitive impairment and dementia have potential as therapeutic targets. Telomeres, which cap chromosomes and act as a 'mitotic clock,' could be promising biomarkers of cognitive aging. Shortened leukocyte telomere length (TL) is linked to accelerated aging and risk factors for AD, and some studies also associate reduced TL with an increased risk of cognitive decline and AD. Human telomerase activity (TA) has also been linked to AD mechanisms.

Innes et al (2018) investigated the effects of two relaxation programs, Kirtan Kriya (KK) meditation and music listening (ML), on telomere length (TL), telomerase activity (TA), and amyloid-beta (Aβ) levels in adults with subjective cognitive decline (SCD).

The KK group showed significantly greater increases in plasma Aβ40 levels compared to the ML group. Both groups showed significant increases in TL and TA, with greater increases observed in participants with lower baseline values. TA also showed a significant positive correlation with practice adherence.

Both groups showed significant improvements in memory, cognitive function, and psychosocial status at 3 and 6 months. The KK group exhibited greater improvements in stress, well-being, mood, and QOL-mental health.

This study is important because it suggests that both meditation and music listening can have beneficial effects on cognitive function and well-being in adults with SCD. These activities are also accessible to people of all body types, making them a promising non-pharmacological intervention for cognitive decline.

Effects of Aromatherapy

Aromatherapy is a non-pharmacological treatment for dementia patients that involves the use of essential oils extracted from plants. The mechanism of action for aromatherapy is not fully understood, but it is thought to involve smell molecules interacting with specific receptors in the olfactory system, affecting the limbic system, amygdaloid body, and cognitive function.

The present study investigated the effects of aromatherapy on dementia patients (Daiki 2010). Patients were exposed to the aroma of lemon and rosemary essential oil in the morning and lavender and orange essential oil in the evening. The study found that aromatherapy improved abstract idea formation and movement, and cognitive function showed overall improvement in the entire group. Patients with moderate AD exhibited slight improvement in cognitive function.

The study's findings suggest that aromatherapy may be an effective non-pharmacological treatment for AD patients. However, more research is needed to confirm these findings and the effectiveness of aromatherapy alone/paired with other medications.

Efficacy of Brexpiprazole as AD Medication

As Alzheimer's disease (AD) progresses, patients may experience increased agitation and aggression. This can be a challenging and disruptive symptom for both patients and caregivers.

Brexpiprazole is a medication that is effective and well-tolerated in treating agitation in patients with schizophrenia and major depressive disorder (Grossberg 2019). It works by acting on various neurotransmitters, including serotonin, dopamine, and noradrenaline.

Grossberg et al (2019) was a study conducted to see if brexpiprazole could also be effective in treating agitation in patients with AD. The study included patients with moderate AD who were experiencing agitation. Patients were randomly assigned to receive either brexpiprazole 2 mg/day, brexpiprazole 1 mg/day, or a placebo.

The study found that brexpiprazole at a dose of 2 mg/day was more effective than a placebo in reducing agitation in patients with AD. However, the 1 mg/day dose of brexpiprazole was not as effective as placebo. These findings suggest that brexpiprazole may be a promising treatment option for the agitation and aggression symptoms in patients with AD.

Effect of Levetiracetam as AD Medication

Levetiracetam, commonly used to treat seizures, has shown potential in improving cognitive function in Alzheimer's disease (AD) mouse models and is effective in suppressing seizures in AD patients with seizure disorders. Vossel et al. (2021) aimed to investigate its impact on cognitive function in AD patients, specifically comparing those with epileptiform activity to those without.

Eligible participants were adults under 80 years old diagnosed with probable AD. Initially, the study focused on participants with symptom onset before age 70 and a history of seizures or epileptiform activity within 5 years. However, the criteria were later expanded to include participants up to age 80 without such history to increase recruitment.

Executive function was assessed using the NIH-EXAMINER, and the tasks evaluated included antisaccade, set-shifting, flanker task, dot counting, category fluency, and letter fluency. The Stroop test measured selective attention, cognitive flexibility, and processing speed. The ADAS-Cog evaluated global cognitive functioning, and a virtual route learning test assessed navigation learning.

In this clinical trial, low-dose levetiracetam was well tolerated in AD patients. Although it did not improve cognitive functioning for all participants, those with epileptiform activity showed cognitive function improvement. Levetiracetam enhanced spatial memory and executive functioning tasks with a good safety profile.

Effect of Methylphenidate on Apathy in AD Patients

Apathy is a common and disabling symptom of Alzheimer's disease (AD), affecting up to 71% of individuals with dementia. It is characterized by diminished initiative and interest in activities, leading to various negative outcomes for patients and caregivers. Currently, there are no proven

treatments for apathy in AD, but methylphenidate, a catecholaminergic agent, has shown promise in smaller studies (Mintzer 2021).

Mintzer et al (2021) investigated its efficacy on a larger scale to better understand if this is a viable medication to alleviate apathy symptoms in AD patients.

To be eligible for the study, participants had to meet specific criteria, including a diagnosis of possible or probable Alzheimer's disease, a score between 10 and 28 on the MMSE, and clinically significant apathy for at least 4 weeks.

The study drug, either generic methylphenidate (5 mg capsules) or placebo (cellulose capsules), was given to participants twice a day. Initially, they received 1 capsule twice a day (10 mg/d for the methylphenidate group) for 3 days, and then the dose was increased to 2 capsules twice a day (20 mg/d) for the rest of the study. The study physicians were able to adjust the dose if participants experienced any adverse events.

In this study, methylphenidate treatment led to a modest but noticeable reduction in apathy among patients with AD, as measured by the NPI apathy subscale. This improvement was observed after 2 months of treatment and was sustained over 6 months.

Efficacy of rTMS on AD Patients

Repetitive Transcranial Magnetic Stimulation (rTMS) is an emerging non-invasive therapeutic strategy. In an rTMS session, an electromagnetic coil is placed at the scalp of the patient’s head to send magnetic pulses that stimulate neurons in certain brain regions. It is generally known as a treatment for major depression. However, in the present study, researchers believe that targeting the precuneus, a key node in the default mode network, with rTMS may help slow down cognitive decline in patients with mild-to-moderate Alzheimer’s disease.

In Koch et al (2022), a 24-week randomized clinical trial was conducted in which researchers investigated the safety and efficacy of precuneus stimulation in 50 patients with Alzheimer’s disease. The mean age of the participants was 73.7 with 52% women. Patients received either real precuneus rTMS or ‘sham’ treatment. The trial consisted of a 2-week course with daily rTMS (or sham) applied five times per week, followed by a 22-week maintenance phase with weekly stimulation.

The primary outcome measure was the Clinical Dementia Rating Scale–Sum of Boxes, but secondary outcome measures included score changes in the Alzheimer’s Disease Assessment, MMSE, and Alzheimer’s Disease Cooperative Study–Activities of Daily Living scale.

Additionally, researchers used single-pulse TMS combined with EEG to assess neurophysiological changes in precuneus cortical excitability and oscillatory activity.

The results revealed that patients who received precuneus rTMS showed stable performance in the Clinical Dementia Rating Scale–Sum of Boxes, while patients in the sham group experienced a worsening of their score. The precuneus stimulation group also demonstrated significantly better performances in the secondary outcome measures compared to the sham group.
In conclusion, 24 weeks of precuneus rTMS may effectively slow down cognitive and functional decline in Alzheimer's disease patients. For future studies, the treatment period should be extended or shortened to understand how crucial of a role duration plays.

Efficacy of tACS at Gamma Frequency on AD Patients

Transcranial Alternating Current Stimulation (tACS) is a non-invasive device that delivers a gentle, sinusoidal electrical current to the brain via electrodes on the scalp. This painless technique aims to enhance the brain's natural oscillations, potentially offering therapeutic benefits for treating diseases or improving brain function.
Recent research indicates gamma desynchronization as a potential additional therapeutic target. AD can also be characterized by disrupted oscillations in the gamma frequency. Noninvasive brain stimulation, like tACS, has shown promise in restoring gamma oscillations and improving cognitive performance.

This study aims to target the precuneus with tACS to understand if it would improve memory tasks and cholinergic neurotransmission as well as investigate brain activity modulation (Benussi 2022).

In this study, 60 patients with Alzheimer's disease (AD) participated in a randomized, double-blind, sham-controlled, crossover design. The diagnosis was corroborated by either cerebrospinal fluid (CSF) analysis or positive amyloid‑positron emission tomography (PET) scan. They underwent a comprehensive clinical and neurophysiological evaluation, including assessments of episodic memory and cholinergic transmission. After 60 minutes of treatment with γ‑tACS targeting the precuneus or sham tACS, the patients were reevaluated. In a subgroup of 10 patients, EEG analysis and personalized modeling of electric field distribution were performed.

The results confirm and expand on previous findings, indicating a potential episodic memory improvement effect of precuneus γ‑tACS in AD patients. Electrophysiological changes were also observed after γ‑tACS stimulation in AD patients. It showed that tACS increased beta power activity in posterior brain regions, and decreased theta power activity in anterior brain regions, thus improving memory.

Efficacy of DBS on AD Patients

Deep brain stimulation (DBS) is a neurosurgical procedure that involves implanting electrodes into specific areas of the brain. These electrodes are then connected to a pulse generator, which is implanted under the skin in the chest. The pulse generator sends electrical impulses to the brain, which can modulate the activity of neurons in those areas. It is a more invasive procedure compared to rTMS, but it is highly effective. Due to its high efficacy in treating a variety of movement disorders, including Parkinson's disease, essential tremor, and dystonia, researchers are beginning to shed light on its potential as a treatment for degenerative disorders like AD.

In Sankar et al (2014), researchers used DBS to stimulate the fornix, the primary outflow tract from the hippocampus to understand its potential in slowing cognitive decline.

The methods of the present study were discussed in detail in Laxton et al (2010). Essentially, they selected men or women aged 40-80 years with a probable Alzheimer's diagnosis within the past 2 years, a Clinical Dementia Rating (CDR) score of 0.5 or 1.0, and a MMSE score between 18 and 28. Cognitive measures, including word recall and word recognition tests, were used as well. PET scans were conducted before and after 12 months of DBS treatment to measure glucose metabolism in the brain. Researchers also used structural MRI to assess one-year changes in hippocampal, fornix, and mammillary body volume.

Through MRI, researchers observed that the hippocampus volume increased over 12 months in certain AD patients when they received DBS in the fornix region. These volume increases in the hippocampus were associated with higher relative glucose metabolism in the hippocampus. This study is significant as it introduces a novel approach to treating AD. Unlike other studies that mainly rely on memory tests, this unique research employs brain scanning techniques (PET, MRI) to offer concrete evidence of brain changes. This provides a more objective and reliable assessment of the treatment's effects on AD patients.

Conclusion

Alzheimer's disease, a neurodegenerative disease, is increasingly prevalent worldwide, particularly in the United States. Presently, over 6 million people have been diagnosed with AD, and it is disheartening that a cure has not yet been found. Nevertheless, researchers are diligently exploring novel treatments aimed at mitigating symptoms like memory loss and cognitive decline. This review encompasses a wide array of approaches, ranging from nonpharmacological methods like exercise, creative therapy, and music listening to medication and brain stimulation. Remarkable strides have been made in comprehending AD and its potential treatments, instilling

hope that ongoing advancements in technology will eventually lead to a cure for this devastating disease.

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